REPORT

health technology assessment

SCREENING FOR CONGENITAL HYPOTHYROIDISM

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EXECUTIVE SUMMARY

The birth prevalence of congenital hypothyroidism for Malaysia has been estimated to be in the region of 1 in 2 500 to 1 in 3 500 live births. Thus, in 1996 for example, 180 children would have been born with congenital hypothyroidism. The majority of these children would have been detected late, and would already have had moderate to severe mental retardation. Mass screening of the newborn for congenital hypothyroidism will allow diagnosis and treatment of nearly all infants with congenital hypothyroidism before the appearance of clinical features. Intelligence remains within normal range if treatment begins before the age of one month.

The cost-benefit ratio in relation to detecting and treating congenital hypothyroidism compared to the productivity of the treated child is 1: 8.9, meaning that society gets a returns of approximately USD 8.90 for each dollar spent on congenital hypothyroidism screening. A nationwide congenital hypothyroidism screening program, once established, should produce a savings to society of U$ 50 million per year.

With respect to local costing, based on 523 324 live births and an estimated incidence of 1:3 000 per year, the total cost of a screening programme would be about RM 3 172 037 annually (taking into account only the costs of reagents and cost of recall). It is estimated then that about 175 cases of congenital hypothyroidism will be detected annually. The cost of treatment of these cases is estimated to be RM 5 652 annually or RM 451 710 over their whole life span.

There is sufficient evidence to indicate that screening for hypothyroidism is safe, effective, and cost-effective. Adequate coverage can be obtained by tagging on to the existing neonatal screening programme for G6PD, without the need for additional work, time and manpower.

It is recommended that a national screening programme for congenital hypothyroidism coordinated by hospital paediatric departments be instituted. TSH testing using cord blood serum should be carried out, with supplementary T4 testing for borderline samples. These tests can be conducted at state hospitals.

For patients with congenital hypothyroidism, the recommended treatment guidelines should be followed.

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SCREENING FOR CONGENITAL HYPOTHYROIDISM

1. INTRODUCTION

Neonatal hypothyroid screening or screening for congenital hypothyroidism was first introduced more-than two decades ago in 1974 in North America and the United States (Fisher et al, 1979). It is now an established national programme in many industrialised countries; in Europe from 1974 to 1979 (Virtanen et al, 1984; Delange et al, 1980), United Kingdom in 1982 (Barnes, 1979; Grant et al, 1988), Australia and New Zealand in 1983 (Human Genetics Society of Australia Newborn Screening Committee, 1985), Hong Kong in 1984, 1986 (Lam et al, 1986) and Singapore in 1989 (Joseph, 1991). Apart from Singapore and Hong Kong, congenital hypothyroid screening is not being done routinely on a nation-wide scale in the South East Asian region. Malaysia, too, has yet to develop a national screening programme for this condition.

The burden of illness (or size of the problem) that congenital hypothyroidism poses is an important consideration in establishing a screening programme (Hall 1995). Wilson & Junger suggests that for any condition to merit screening "the condition to be sought should be an important health problem as judged by the potential for health gain achieved by early diagnosis" (Hall 1995).

A screening programme can be viewed as an instrument that should pay for itself. This could be achieved by reducing future health services costs by a greater (present) value than the cost incurred by the programme. If the programme costs are higher than the future cost savings, the value of reduction in morbidity may justify the screening programme. In brief, the cost of a screening programme should include:

- The cost of screening
- The cost of unnecessary treatment due to the screening programme having less than 100% specificity
- Treatment cost
- Cost of care in the public sector
- Cost of care in the private sector

The two relevant issues in this context are how common congenital hypothyroidism is (birth prevalence) and what the impact of early treatment of the condition is. The phrase "birth prevalence" is used instead of just "prevalence" because the true prevalence cannot be known. This is because some births will end up as stillbirths while others may die later (early neonatal deaths).

Data on the birth prevalence of congenital hypothyroidism, though still limited, began to become available since the 1980s. An examination of the published data on the birth prevalence of congenital hypothyroidism from various industralised countries and regional countries shows some variation in prevalence. This has some bearing on the situation in Malaysia.

Congenital hypothyroidism causes mental retardation that can be prevented by prompt proper treatment. At least 75% of cases not detected and treated before 3 months old result in appreciable mental retardation. Severe mental retardation results in 1%-2% of all admissions to institutions.

2. OBJECTIVE

To determine safety, effectiveness and cost effectiveness of screening for Congenital Hypothyroidism.

3. METHODOLOGY

The database used was MEDLINE using the Internet. In addition, local unpublished data was obtained from researchers in the field. The key words used in the search were *congenital hypothyroidism, screening, outcome, early treatment,* and *prevalence*. These words were used either singly or in various combinations. The years searched were from 1966 – 1998. A total of 516 titles were first identified. These were then further refined and subdivided as follows:

3.1 Articles related to "Burden of Illness":

- Relevant titles = 29
- Papers reviewed = 17
- Abstracts reviewed = 2
- Additional papers & books reviewed = 5
- Total articles reviewed = 24

3.2 Articles related to "Outcome with and without screening and early treatment."

- Relevant titles = 15
- Papers reviewed =13
- Abstracts reviewed = 2

Each of the above articles was then graded on the level of evidence according to the modified CAHTA scale (Appendix A)

4. RESULTS & DISCUSSION

4.1 Burden of Illness/Birth Prevalence

Data from industrialized countries shows a birth prevalence of congenital hypothyroidism ranging from 1 in 3500 to 1 in 4000 live newborns (Barnes, 1985) as shown below:

Country	Birth prevalence	Source
United Kingdom	1 in 3937	Grant, 1988
North America	1 in 3700	Willi, 1991
France	1 in 4041	Dhondt, 1991
Australia	1 in 4253	Special Report 1983
New Zealand	1 in 4867	Special Report 1983

This range is best illustrated by data from 14 European countries (73 centres) that showed collective birth prevalence of 1:3598 but with an inter-country variation of 1:2860 in the Netherlands to 1:5770 in Austria (Delange 1998). Hence, there is no evidence to suggest that the birth prevalence in any one country should be similar to the collective prevalence in Europe or even to that in the USA. Some of these variations, however, may be due to limitations in the sample sizes.

In the Asian region, the reported birth prevalence's (Amar, 1997) are as follows:

Country	Birth prevalence	Source
Hong Kong	1 in 2903	Low 1986
Thailand	1 in 3843	Rajatanavin, 1993
China	1 in 4584	Zhang, 1993
Singapore	1 in 2007	Joseph, 1991
Pakistan	1 in 1000	Akhani, 1989
India	1 in 2481	Desai, 1987

For the Malaysian situation, data from three local studies showed a birth prevalence of 1 in 2410 (Harun, 1992), 1:3666 (Wu et al, 1999) and 1:2983 (Amar, 1997). Pooled data from the studies in the Asian region suggest a birth prevalence of 1 in 3093 for the South East Asian region as a whole (Amar, 1997). The number of newborns screened in the various Asian and Malaysian studies quoted ranges from 5,000 to 91,000 with the majority of studies having less than 30,000 samples. Since the birth prevalence of congenital hypothyroidism is low, statistical analysis of the screening data indicates that the number of newborns screened determines the validity of the figures quoted i.e. the 95% confidence interval for the range of the "true" prevalence is wide (Amar, 1997, Rosenthal, 1988). Hence, the "true" birth prevalence of congenital hypothyroidism for these countries and for Malaysia too, has yet to be determined accurately, but may be in the region of 1 in 2500 to 1 in 3500.

Generally, the birth prevalence of congenital hypothyroidism appears to be higher in Asian countries (including Malaysia) when compared with Europe or America. The prevalence figures above show a wide variation among countries, and the overall pooled rate is lowered by data from China. Further, these higher rates have been supported by work in industrialized countries. Studies in the United Kingdom have shown a higher birth prevalence of congenital hypothyroidism in Asians (1 in 918) when compared with non-Asian (1 in 3391) (Brown, 1986) [Asians in this context are Indians, Pakistanis and Bangladeshis]. In addition, studies in the USA have suggested an increased incidence in Orientals of 1 in 2128, as compared to the general population (Fisher, 1991). There may

be three possible reasons for this increase. It could be partially explained by consanguinity, which is more common among certain ethnic groups in the region. However, the majority of cases in these studies were not due to inherited defects (thyroid dyshormonogenesis) but due to thyroid digenesis. A second explanation is transient primary hypothyroidism due to iodine deficiency. It is well recognised that iodine deficiency can affect the results of screening tests (Fisher, 1991). Countries in the Asian region have, to varying degrees, the problem of iodine deficiency. Finally, the higher prevalence rates could be reflecting the true genetic situation in the region.

What does the burden of disease mean in real terms? Using the estimate from pooled data of studies in the Asian region (1 in 3093) together with the number of live births of 556,745 in Malaysia for 1996(Ministry of Health, 1998), 180 children would have been born with congenital hypothyroidism in that year (Amar, 1994). In the absence of a screening programme, the majority of these children would have been detected late, and would already have had moderate to severe mental retardation (Amar, 1994).

4.2 Approaches to Screening

There is no consensus in the approach to screening for congenital hypothyroidism. (Lakhani et al, 1989; Low et al. 1986; Desai et al.1987; Amar et al, 1977; Amar, 1997 ; Wu et al, 1999).

An effective screening strategy is to not only choosing a method that is effective in terms of early recall and treatment with low false positive and no false negative rates, but also one that can be included into already existing established screening programmes of each country. The screening methodology thus differs from country to country with respect to
(i) site of sample collection - cord blood or capillary heel prick
(ii) timing of sample collection
(ii) test strategies, and
(iii) recall criteria.

4.2.1 Site of sample collection

Cord blood collected in specimen tubes is the common approach adopted by many Asian countries except for Pakistan (Lakhani et al, 1989), China (Zhang et al, 1993) and in a pilot study in Maternity Hospital Kuala Lumpur (Wu et al, 1999) where dried bloodspots on filter papers were used.

The coverage with using cord blood collection at birth is good in most Asian countries (Rajatanavin et al, 1993; Low et al, 1986; Desai et al, 1987; Amar et al, 1977; Joseph et al, 1991). For example, Thailand had coverage of 88%, while Hong Kong and Singapore had more than 99% coverage. A pilot project in Perak, Malaysia, showed coverage of 91%. The missed cases were attributed to stillbirths, sample lysis, insufficient blood samples and samples not being collected (Amar et al, 1977). In India, the coverage was only 72%. Here, the cases missed were attributed to heavy workload, negligence and indifferent attitude of staff, spoilt samples and poor organisation. The coverage is expected to be good in countries where there is an existing neonatal screening programme for G6PD as in Singapore, Malaysia, and Hong Kong. (Joseph et al, 1991).

Adequate coverage can be improved by tagging to the existing neonatal screening programme for G6PD in Malaysia, Singapore, and Hong Kong without imposing extra work, time and manpower (Desai et al, 1987; Joseph et al, 1991).

4.2.2 Timing of sample collection

Capillary bloodspots on filter papers are usually sampled between 3rd to 8th days of life in the Western countries where neonatal hypothyroid screening is practiced. This is to avoid false positives due to physiological surges of TSH after birth, especially during the first 48 hours after birth (John, 1987). However, this method is not practical in most Asian countries, since there is usually early discharge after delivery and there are limitations of human resources to ensure adequate coverage of all babies delivered after discharge. In addition, there is often much mobility of parents and babies after the delivery, cultural taboos against blood taking in the babies, and parental reluctance. Thus, the Western approach may not be effective, and cord blood sampling at birth may be the preferred method.

4.2.3 Test strategies:

Three approaches have been used:

- primary T4 measurement supplemented by TSH
- primary TSH measurement supplemented by T4
- combined T4 and TSH measurement.

In screening for congenital hypothyroidism patients may need to be recalled for various reasons. The recall rate may depend on the following

- timing of blood sampling
- the screening approach
- the sensitivity and specificity of the tests.

The different tests have varying recall rates as indicated below:

Screening tests	Recall rate
T4	6.12%*
TSH	0.11-5.4%**
Combined T4 & TSH	*1.7-3.3% ****

*Lakhani et al, 1989

**Lakhani et al, 1989 Rajatanavin et al, 1993; Low et al, 1986; Desai et al, 1987; Zhang et al, 1993; Amar et al, 1977; Wu et al, 1999

****Harun et al, 1992; Joseph et al, 1991.*

4.2.4 T_4 & TSH measurement

Most N. American, Australian and New Zealand programmes use a T_4 and sequential TSH measurements (Fisher et al, 1979; Grant et al, 1988; Joseph et al, 1991; Watfish, 1976; American Academy of Pediatric Section on Endocrinology & Committee on Public

Health, 1993). Europe, Japan, Singapore and Hong Kong use TSH and sequential T_4 measurement, (Virtanen et al, 1984; Barnes, 1979; Grant et al, 1988; Lam et al, 1986; Dussault, 1997).

This involves using a filter paper blood spot T_4, together with a TSH measurement in those specimens with low T_4 values. The cut off point for low T_4 concentrations is - 2.1 SD (standard deviation) from the geometric mean of assays of the same day (usually 7 mcg/dl), or, T_4 values less than 10^{th} centile.

Some programmes have reported cases of low or normal T_4 with high TSH, in which case the cut-off T_4 values is raised to 20^{th} centile. The advantage of this strategy is that it could detect all types of hypothyroidism, including thyroxine binding capacity (TBG) deficiency (Fisher et al, 1979). The incidence of the different types is reported to be as follows:

Type of deficiency	Incidence
Secondary congenital hypothyroidism	1: 60,000
Tertiary congenital hypothyroidism	1: 1000,000
Transient congenital hypothyroidism	1: 37,370
TBG deficiency	1: 50,000-8913

The disadvantage of this strategy is the high recall rate of between 0.1-3.5% (Fisher et al, 1979; Virtanen et al, 1984; Fisher, 1987; John, 1987; Joseph et al, 1991). Among the numerous causes of false - positive T_4 screening values are prematurity and low birth weight babies (Virtanen et al, 1984).

4.2.5 TSH and sequential T_4 measurement

Primary TSH approach is the most commonly adopted strategy among Asian countries (Rajatanavin et al, 1993; Low et al, 1986; Desai et al, 1987; Zhang et al, 1993; Amar et al, 1977; Amar, 1997). It is sensitive and is least expensive compared to others such as primary T4 or combined TSH and T4 approach. Although this method may miss cases of congenital hypothyroidism due to hypothalamic-pituitary deficiency, this is a very rare condition.

Using this approach, the cut off values for the purpose of recall would depend on the timing of blood sampling. In Europe and Japan blood samples are taken after the 5^{th} day of life and the cut off TSH level used is 25 mu/L. In countries where babies are discharged early after delivery in hospital e.g. Finland (Virtanen et al. 1984), cord blood TSH is taken, and the cut off TSH value for recall are as follows:

(i) TSH >59 mμ/L and

(ii) TSH 45-59 mμ/L, T4 <120 ηmol/L (less than - 2 SD).

The recall rate varies depending on the timing at which blood was taken, and the method of diagnostic TSH assay used. However, recall rate is also dependent on the recall criteria used. These criteria's for primary TSH screening varies amongst studies depending on

the frequency distribution of cord blood TSH results. The affected hypothyroid babies usually have TSH values > 97th percentile of normal TSH distribution (Rajatanavin et al, 1993; LCK Low et al, 1986; Desai MP et al, 1987). Some studies have found a recall rate of 0.03 % to 0.12 % (Delange F et al, 1980; Fisher DA et al, 1979; Lam STS et al. 1986).

In Pakistan, a cut-off TSH value of >20 μIU/ml was able to detect all the confirmed cases of congenital hypothyroidism (Lakhani et al, 1989). In Hong Kong the same cut-off value would have missed 2 cases (28%) of hypothyroid babies who had cord blood TSH of 15-20 μIU/ml (Low et al, 1986). In India, all the confirmed cases of congenital hypothyroid had a TSH value of less than 80 μIU/ml. The pilot studies in Malaysia showed cord blood TSH of >80 μIU/ml (LL Wu et al., 1999), >60 μIU/ml (Amar et al., 1977), >50 μIU/ml (Harun et al., 1992) in the all the confirmed cases except in University Hospital where there was one baby with a cord blood TSH of 15 μIU/ml who was missed and would had been missed just the same by any other screening approach and recall criteria (Harun et al., 1992). In Singapore, 80% of the congenital hypothyroid babies had a cord blood TSH of greater than 50 μIU/ml and 20% had a TSH 23-50 μIU/ml. False positive high cord blood TSH levels have been found in difficult deliveries, vacuum extraction, premature deliveries and others.

The newer enzyme-linked immunoassays - chemiluminescent assays - are more advantageous because of greater sensitivity than radioactive labels (Dussault et al, 1983). The disadvantage of this strategy is that it can only diagnose primary hypothyroidism (secondary and tertiary congenital hypothyroidism are not detected) and it will also miss detecting those who truly have hypothyroidism but where the rise in TSH (1: 100,000) is delayed due to premature development of pituitary thyroid axis. The methods using TSH are less expensive and more sensitive than those using T_4.

4.2.6 Combined T_4 - TSH measurement

This is the ideal strategy because screening using either primary T_4 or TSH, 5-10% of neonates with congenital hypothyroidism would be missed (Dussault et al, 1983; Dussault, 1997), due to biological variants (this is normal for screening hormone programmes). However, this would be an expensive option.

4.2.7 Recall

A study in India showed that the recall rate is lowest (1.42%), using the primary TSH approach and high using both the T_4 (6.12%), and combined T_4 & TSH (7.42%) approach (Lakhani et al, 1989).

The responses to recall have been generally poor among the Asian population. Mobility of population, false addresses, ignorance, poverty and cultural believes and taboos are some of the reasons. Even in countries with high literacy rates such as Hong Kong, the response to recall was only 71%. The responses to recall in India were quoted to vary

from 30-100%. In Malaysia, the response to recall is difficult in selected regions of the country but it is excellent in the majority of the regions (Amar et al, 1997).

4.3 Outcome in the Absence of Screening and Early Treatment

The morbidity of congenital hypothyroidism in the absence of screening was illustrated in a retrospective study done locally in Penang, Malaysia (Tan et al, 1994) where over a 15 years period, 26 cases of congenital hypothyroidism were seen. Considering the developmental quotient in these children, it was found to be appropriate for their chronological ages at diagnosis in less than one-third of the patients, while school performance was at least average in only less than a third of the school-goers.

The outcome of congenital hypothyroidism in the absence of screening and, hence, without early treatment, was also illustrated in the paper by Hulse (1981) where he described the findings of 141 hypothyroid children before the existence of a screening programme. The mean IQ of these 141 children was 79.5, it being normal in 6 children diagnosed before 6 weeks of age. In addition to a decline in IQ, these children had multiple learning difficulties; i.e. in reading, spelling and writing. Clumsiness and mental retardation was present in 25% of these children and 29% had to attend special school whilst 43% possessed deviant behaviour.

4.4 Outcome With Screening And Early Treatment

Mass screening of the newborn for congenital hypothyroidism will allow diagnosis and treatment of nearly all infants with congenital hypothyroidism before the appearance of clinical features. It has been shown (Vitranen et al, 1983) that intelligence remains within normal range if treatment begins before the age of one month, as part of the neurological damage seems to occur before birth. If treatment was delayed until about three months of age, there was neurological, developmental and psychometric retardation. In the United Kingdom, because of their national screening programme (Grant, 1984), children with congenital hypothyroidism were started on treatment at a median age of seventeen days. As a result of the Finnish national screening (Vitranen et al, 1984), the median age at start of treatment was six days. Provided treatment is started early (before six weeks of age) there is no significant effect of age at which treatment was started on the subsequent IQ of the children (Lancet, 1996).

As a result of mass screening and early intervention at 25 $\pm$ 15 days before the appearance of clinical manifestations (New England Collaborative Group, 1981), children were found to have a normal IQ - higher than 79.5 (Hulse, 1984; Glorieux et al , 1985). The mental development of these children at 5 and 7 years of age was found to be satisfactory, with only 10% having a developmental quotient less than 90%, with the performance and practical reasoning scales being most discriminant (Glorieux et al, 1985). Neuropsychological functions at 6 years of age showed no difference in these children when compared to controls except in the speed of motor function (New England Congenital Hypothyroid Collaborative, 1985). However, neonates with early clinical features indicative of severe congenital hypothyroidism had poorer intellectual prognosis

(New England Collaborative Group, 1981). Other factors resulting in a low IQ are initial T4 and T3 levels, bone maturation at diagnosis, presence or absence of thyroid tissue and inadequate treatment (Lancet, 1996).

4.5 Treatment of Congenital Hypothyroidism

In treating patients with congenital hypothyroidism, the American Academy of Paediatrics recommend 10-15μg/kg/day, while infants with very low or undetectable T_4 concentrations should receive 50 μgms daily. The serum T_4 concentrations should be maintained at all times in the upper half of normal range during the first 3 years of life (American Academy of Paediatrics, 1993). The time required to normalise serum T_4 concentrations during therapy with thyroxine has varied from an average of 74 days from the time treatment was begun using a 7-9 μg/kg/day dose, to 31 days for an 8-10μg/kg/day dose, and to less than 3 weeks for a 10-15μg/kg/day thyroxine dose. Assuming a 3-week average delay in starting treatment, the average age for normalisation of the serum T4 level would approximate 3 months, 2 months and one and a half months respectively for a 7-9, 8-10, and 10-15μg/kg/day thyroxine dose (Amar, 1997).

Most children diagnosed as a result of neonatal screening who have been started on adequate treatment at an early age will not have any learning problems. Overall, neonatal screening for congenital hypothyroidism has already proven to be an unqualified success (Lancet, 1996).

4.6 Economic Aspects

The important benefits with a screening programme for hypothyroidism are those accrued by avoidance of the burden to society with respect to cost of caring for the mentally retarded child and adult. This would include institutionalised care, special education, and other special needs. There is also improved well being of the affected child as well as the parents. With respect to cost implications, a screening programme using the primary TSH approach covering 500 000 annual births would cost approximately RM 7.6 million (US $ 2 million) [Amar, 1997].

The survival rate of congenital hypothyroidism was postulated to be 95% of those normal children. The average cost per child screened for congenital hypothyroidism is U$1.55. With an incidence of one in 6 000 live birth in US, the cost of detection of a single case of congenital hypothyroidism will be about U$ 9 300. The cost of a treatment programme for those with congenital hypothyroidism adds a present value U$2 500, yielding a total overall cost of U$11 800.

The per capita institutional cost for the mentally retarded in US in 1997 averaged U$13052 per year. The cost of special education for the mildly retarded are 1.9 times that of normal children, while more intensive programmes for the moderate to severely retarded averaged 3.5 times the cost for normal children.

With a retarded child at home from the age of 4 to 25 years, it will be half as likely for the mother to work in comparison to those with normal children. The average

productivity of persons with congenital hypothyroidism was estimated to be 60% of the normal mean productivity of that of persons in the labour force.

The cost-benefit ratio in relation to detecting and treating congenital hypothyroidism compared to the productivity of the treated child is 1: 8.9, meaning that society gets a returns of approximately U$8.90 for each dollar spent on congenital hypothyroidism screening. A nationwide congenital hypothyroidism-screening programme once established should produce a savings to society of U$ 50 million per year.

5. LOCAL SITUATION

While there is an absence of a national screening programme for congenital hypothyroidism, there have been some efforts made in this area. A research project was carried out in Perak in 1995. Pilot projects were also carried out in University Hospital Kuala Lumpur (1987 - 1990) and Kuala Lumpur Hospital in 1995. Recently more pilot projects have been carried out.

5.1 Pilot Project

The Ministry of Health launched a pilot project in Ipoh, Seremban, Tengku Ampuan Rahimah Klang and Port Dickson hospitals in October 1998. An evaluation carried out in October 1999 showed that 24 687 babies were screened, and 7 cases of congenital hypothyroidism were identified. Most laboratory results were available within 12 - 48 hours, others within a maximum of 3 days. Testing was carried out with existing TSH and T_4 testing equipment already available in these hospitals. Most hospitals use fully automated immunochemistry analysers using chemiluminescent technology. The false positive rate that resulted in recall was 0.3%. The paediatrics departments in the state hospitals coordinated the screening, while the obstetrics departments carried out sample collection. Screening results were sent to the paediatrics department for decisions on recall and subsequent management of these patients. The public health services coordinated follow-up of patients for recall and collection of blood for home deliveries. All recalled patients were seen within 10 days of birth. Treatment was started in all cases of congenital hypothyroidism within 2 weeks of life.

Overall, the pilot project worked well. This pilot project was extended to cover two additional hospitals - Malacca and Kota Bharu hospitals - in April 1999

5.2 Local Costing

For local costing, based on 523 324 live births and an estimated incidence of 1:3000 per year, the total cost of a screening programme works out to about RM 3 172 037 annually (taking into account only the costs of reagents and cost of recall). It is estimated that with this, about 175 cases of congenital hypothyroidism will be detected annually. The cost of treatment these cases is estimated to be RM 5 652 annually or RM 451 710 over their whole life span (please see Appendix B for detailed costing).

On the other hand, if there is no screening for congenital hypothyroidism, and consequently no treatment is instituted, the loss of productivity is RM 2 117 850 annually. In addition, the direct costs involved are the costs of special schools for the mild and moderately mentally retarded, as well as other rehabilitation costs for which detailed local costing is not readily available. The indirect costs that need to be taken into consideration are the loss of GNP of mothers who are forced to stay at home to look after children with congenital hypothyroidism who are moderately and severely mentally retarded. Alternatively, there will be costs of hiring special nurses or maids to look after these children.

However, despite the absence of detailed costs in all areas, it is evident that a screening programme for congenital hypothyroidism is cost-effective.

6. CONCLUSIONS

There is sufficient evidence to indicate that screening for hypothyroidism is safe, effective, and cost effective. A number of screening methods are available which have high levels of sensitivity and specificity. However, inevitably 5-10% of cases will be missed due to logistic errors and limitation of the present screening methods.

Adequate coverage can be obtained by tagging on to the existing neonatal screening programme for G6PD in without the need for additional work, time and manpower.

7. RECOMMENDATIONS

It is recommended that a national screening programme for congenital hypothyroidism be instituted. The sample to be used should be cord blood serum. The testing method should be TSH. For borderline samples, supplementary T4 testing should be carried out, to reduce the recall rate.

Testing should be conducted at state hospital level utilising existing TSH assay equipment, using chemiluminesent technology as far as possible. The recommended treatment guidelines should be followed to adequately supplement cases that have been detected. Hospital paediatric departments should coordinate this screening programme for congenital hypothyroidism to facilitate urgent recall of patients and institute early treatment of confirmed cases.

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19. Fisher DA. *Status Report: Screening for Congenital Hypothyroidism.* Trends Endocrinol Metab 1991; 2(4):129-133.

20. Glorieux J, Dussault J.H. et al. *Follow-up at ages 5 and 7 years on mental development by Quebec Screening Program.* The Journal of Paediatrics Vol 107 no 6, Dec 1985; pages 913-915

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30. Lam STS et al. *Neonatal Screening for Congenital hypothyroidism and G-6-D deficiency in Hong Kong.* Hong Kong J. Paediatr 1986; 1: 26-33.

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33. Martti Virtanen et al. *Finnish National Screening for Hypothyroidism.* Eur J Pediatr 1984; 143: 2-5

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43. Willi SM, Moshang T. *Diagnostic Dilemmas: Results of screening tests for congenital hypothyroidism.* Pediatr Clin North Am 1991; 38: 555-566.

44. Wu LL, Sazali BS, Adeeb N., Khalid BAK. *Congenital Hypothyroid Screening Using Cordblood TSH.* Singapore Medical Journal January, Jan 1999

45. Zhang YQ, Cao QX. *Experience in neonatal screening for congenital hypothyroidism.* Chinese Medical Journal 1993; 106(3): 216-219.

9. EVIDENCE TABLES

No	Author, Title, Journal, Year	Study Type, Sample Size, Follow-up	Characteristics & Outcome	Comments & Grade of Evidence
BIRTH PREVALENCE OF CONGENITAL HYPOTHYROIDISM IN INDUSTRALISED COUNTRIES				
1	Barnes ND *Screening for congenital hypothyroidism: the first decade.* Arch Ds Child 1985; 60: 587-92.	General review of screening programmes	- Birth prevalence of congenital hypothyroidism in screening programmes 1:3500-1:4500. - 80-90% due to thyroid dysgenesis.	Poor. Comprehensive paper outlining the state of screening up to that point in time.
2	Grant DB, Smith I *Survey of neonatal screening for primary hypothyroidism in England, Wales and Northern Ireland 1982-84.* British Medical Journal 1988; 296:1355-8.	Audit of all screened neonates in UK for 1982-1984. Sample size 2 million.	- Birth prevalence of congenital hypothyroidism in screening programmes 1:3937. - Outcome of cases identified, onset of therapy detailed.	Good. Extensive & exhaustive analysis of country wide programme.
3	Willi SM, Moshang T *Diagnostic Dilemmas: Results of screening tests for congenital hypothyroidism*. Pediatr Clin North Am 1991; 38 : 555-566.	Analysis of tests used in screening programmes	- Quotes North American birth prevalence of congenital hypothyroidism in screening programmes as 1:3700.	Poor
4	Dhondt JL, Farriaux JP, Saily JC, Lebrun T *Economic evaluation of cost-benefit ratio of neonatal screening procedure for phenylketonuria and hypothyroidism.* J Inher Metab Dis 1991; 14 : 633-9.	A review of economics of screening	- Quotes France's birth prevalence of congenital hypothyroidism in screening programmes as 1:4041.	Poor

No	Author, Title, Journal, Year	Study Type, Sample Size, Follow-up	Characteristics & Outcome	Comments & Grade of Evidence
5	*Special Report: Newborn screening for metabolic disorders in Australia and New Zealand: Results for 1983.* Med J Aust 1985; 143 : 159-60.	Review of data on screening programmes in Australia & New Zealand. Sample >4ml	- Birth prevalence of congenital hypothyroidism in screening programmes 1:4253 for Australia and 1:4867 for New Zealand.	Good. Excellent summary paper.
6	Delange F, Illig R, Rochiccio P, Brock-Jacobsen B *Progress report 1980 on neonatal screening in Europe.* Acta Paediatric Scandinavica 1980; 70:1-2.	Review of data on screening programmes in Europe. 18 countries reviewed - very large samples from 14 (comprising 73 centres)	- Collective birth prevalence of congenital hypothyroidism (14 countries) 1:3598. - Inter-country variation from 1:2860 to 1:5770. - Shows the wide possible variation in prevalence between countries.	Good. Excellent summary paper.
BIRTH PREVALENCE OF CONGENITAL HYPOTHYROIDISM IN THE ASIAN REGION				
1	Amar HSS *Congenital Hypothyroidism Screening in South East Asia.* J Paediatrics, Obstetrics & Gynaecology Jan/Feb 1997; Pg.1-6	Review of screening programmes in the region with data on screening in SE Asia.	- Pooled (combined) birth prevalence from Asian data is 1:3093. - Outlines the approaches taken in various countries s& suggest the way forward.	Fair

No	Author,Title, Journal Year	Study Type, Sample Size, Follow-up	Characteristics & Outcome	Comments & Grade of Evidence
2	Low LCK, Lin HJ, Cheung PT, Lee FT, Chu TL, et al *Screening for congenital hypothyroidism in Hong Kong.* Australian Paediatric Journal 1986; 22:53-6.	Results of screening programme. Sample size 20,319 (7 detected cases).	- Birth prevalence of congenital hypothyroidism in screening programme 1:2903. - Cord blood screening.	Good to fair. Reasonable sample.
3	Rajatanavin R, Sriprapadaeng A, Sompong W, Kongsuksai A, Suebwonglee S, et al *Screening for Congenital Hypothyroidism in Thailand: Has its time come?* J Med Asso Thailand 1993; 76(2):2-8.	Results of screening programme. Sample size data not provided in the article.	- Birth prevalence of congenital hypothyroidism in screening programme 1:3843. - Cord blood screening.	Fair - results not presented well.
4	Hang YQ, Cao X *Experience in neonatal screening for congenital hypothyroidism.* Chinese Medical Journal 1993; 106(3):216-219.	Results of screening programme. Sample size 91,683 (20 detected cases).	- Birth prevalence of congenital hypothyroidism in screening programme 1:4584. - Did not use cord blood, heel prick at 48-72 hours.	Good.
5	Joseph R, Ho LY, Gomez JM, Ikshuvanam M, Aw TC, et al. *Non isotopic cord blood serum screening for congenital hypothyroidism in Singapore - the TSH and T4 strategy*. Wilcken B, Webster D, eds. Neonatal screening in the Nineties. 8th International Screening Symposium, New South Wales, Australia, November 1991, pgs 69-70.	Results of screening programme. Sample size 20,072 (10 detected cases).	- Birth prevalence of congenital hypothyroidism in screening programme 1:2007. - Cord blood screening.	Good to fair. Reasonable sample.

No	Author,Title, Journal Year	Study Type, Sample Size, Follow-up	Characteristics & Outcome	Comments & Grade of Evidence
6	Lakhani M, Khurshid M, Naqvi SH, Akber M *Neonatal screening for congenital hypothyroidism in Pakistan.* J Pakistan Med Assoc 1989; 39(11):282-4	Results of screening programme. Sample size 5,000 (5 detected cases).	- Birth prevalence of congenital hypothyroidism in screening programme 1:1000. - Did not use cord blood, heel prick (? at birth).	Fair. Sample size small.
7	Desai MP, Colaco MP, Ajgaonkar AR, Mahadik CV, Vas FE, et al *Neonatal screening for congenital hypothyroidism in a developing country: problems and strategies.* Indian Journal of Pediatrics 1987; 54(4):571-81	Results of screening programme. Sample size 12,407 (5 detected cases).	- Birth prevalence of congenital hypothyroidism in screening programme 1:2481. - Cord blood screening.	Fair. Sample size small.
BIRTH PREVALENCE OF CONGENITAL HYPOTHYROIDISM IN MALAYSIA				
1	Harun F, Ch'ng SL *Congenital Hypothyroidism in a developing country*. Proceedings of Clinical Thyroidology Meeting, Innsbruck, Austria 1992	Abstract. Results of screening programme. Sample size 19,281 (7 detected cases).	- Birth prevalence of congenital hypothyroidism in screening programme 1:2410. - Cord blood screening using TSH.	Good to fair. Reasonable sample.
2	Amar HSS, Jai Mohan *Screening for Congenital Hypothyroidism: A Regional Pilot Project.* Health Systems Research Report 1997, Ipoh Hospital, Malaysia	Abstract. Results of screening programme. Sample size 8,950 (3 detected cases).	- Birth prevalence of congenital hypothyroidism in screening programme 1:2983. - Cord blood screening using TSH.	Fair. Sample size small.

No	Author,Title, Journal Year	Study Type, Sample Size, Follow-up	Characteristics & Outcome	Comments & Grade of Evidence
3	Wu LL, Sazali BS, Adeeb N, Khalid BAK *Congenital hypothyroidism screening using cord blood TSH.* (Submitted for publication 1998)	Full paper. Results of screening programme. Sample size 11,000 (3 detected cases).	- Birth prevalence of congenital hypothyroidism in screening programme 1:3666. - Cord blood screening using TSH.	Fair. Sample size small. Large drop out of recalled patients (74%)
4	Amar HSS *Screening for Congenital Hypothyroidism: The Argument for a National Programme in Malaysia. Malaysian* J Child Health Dec 1994; Vol 6(2): 70-79	A review of the situation locally and arguments for a local screening programme.	- Burden of illness discussed. - Outlines the approaches taken in various countries & suggests local approach.	Fair
OUTCOME WITHOUT TREATMENT				
1	Tan KK, P Kaur *Late diagnosis of congenital hypothyroidism* ***Congress on Paediatrics* 10-13/6/1994 ; Penang, Malaysia.**	Descriptive study of 26 cases picked up in 15years	- Mean age diagnosed 15.8months (21days to 9years) - 42.3% diagnosed within first 3 months of life - 73.7% diagnosed within 1st year of life - 26.3% after 1st year of life - Development quotient appropriate < 1/3 - School performance average < 1/3	Fair
2	J.A.Hulse	Retrospective	CH is associated with persistent morbidity in	Good

No	Author,Title, Journal Year	Study Type, Sample Size, Follow-up	Characteristics & Outcome	Comments & Grade of Evidence
	Outcome for congenital hypothyroidism Arch Dis Child '84:59 23-30	descriptive convenient sample	many aspects of cerebral function. The adverse effects of prenatal hypothyroidism are largely reversible if treated before age 6 weeks	

No	Author,,Title, Journal Year	Study Type, Sample Size, Follow-up	Characteristics & Outcome	Comments & Grade of Evidence
OUTCOME WITH TREATMENT				
1	New England Congenital Collaborative Group *Effects of neonatal screening for hypothyroidism: prevention of mental retardation by treatment before clinical manifestations* The Lancet 1981:1095-1098	Prospective ; 77cases picked up from screening 336,000 newborn babies over 2 $^{1}/_{2}$ years and followed up to 4 years	- Normal mean and distribution of IQs in treated patients indicate that children adequately treated before the appearance of clinical signs and symptoms are protected against MR - Poor compliance or grossly irregular therapy makes ineffective any possible benefit of early treatment - Neonatal screening can't protect all of the 3-4% of infants born with obvious signs and symptoms even when treatment was started at day 5-6; suggesting that it is the thyroid deficiency when treatment is begun rather than the age of the patient that determines the intellectual prognosis	Good Definitely higher IQ than mean of 79.5 for CH diagnosed without screening

No	Author,,Title, Journal Year	Study Type, Sample Size, Follow-up	Characteristics & Outcome	Comments & Grade of Evidence
2	J Glorieux, J H Dussault et al *Follow up at ages 5 and 7 years on mental development by Quebec Screening Program* ***The Journal of Pediatrics*** Vol 107, no 6. Dec 1985 Pages 913-915	Descriptive sample size 5yrs-36 7yrs-25 control of 45 for 5yr gp; no control for 7yr gp	1) At ages 7, the mean IQ was 101 2) Only 10% had a developmental quotient <90 with the performance and practical reasoning scales being most discriminant	Fair
3	New England Congenital Hypothyroidism Collaborative *Neonatal hypothyroid screening status of patients at 6 years of age* ***Journal of Paediatrics*** Vol 107 no 6 Dec1985 Pg 915-918	Descriptive, prospective Convenient sample N=56 31 siblings of patients with CH and 28 euthyroid as contrast group.	- No difference in IQ and neuropsychological function except in speed of motor function - No suggestion that the children with CH diagnosed as a result of neonatal screening and treated early and adequately will have any problems with learning	Fair
4	Personal experience	Personal experience	Adequacy of treatment in early infancy	Fair

No	Author,,Title, Journal Year	Study Type, Sample Size, Follow-up	Characteristics & Outcome	Comments & Grade of Evidence
			National cohort of children with congenital hypothyroidism tested at 5yrs showed those with pre-rx level T4 <42nmol/l had mean deficiency of 10 IQ points ; this is in contrast to New England Cong Hypothyroidism Coll[1]: normal IQ except in cases with early clinical features or poor compliance where higher doses of thyroxine given ie 10-15μgm/kg/day (AAP) vs 25 μgms /day Author feels that there is no relationship between starting dose of thyroxine and outcome at 5yrs.	
5	Outcome of screening for congenital hypothyroidism	1996 Lancet editorial	- Most children diagnosed as a result of neonatal screening who have been started on adequate treatment at an early age will not have any learning problems - Overall, neonatal screening for congenital hypothyroidism has already proved to be an unqualified success	Good
6	DB Grant, I Smith *Survey of neonatal screening for primary hypothyroidism in England, Wales and North Ireland1982 –1984* ***BMJ 1988* 296: 1355-1358**	Report on organisation screening programme over 13 years N=488	- Overall incidence 1:3937 births with congenital hypothyroidism - Median age of 17days when treatment was started	Good
7	M Virtaner et al	Effect of age at	- Progressive loss of intelligence potential starts from birth	Good

No	Author,,Title, Journal Year	Study Type, Sample Size, Follow-up	Characteristics & Outcome	Comments & Grade of Evidence
	Congenital hypothyroidism: age at start of treatment vs outcome Acta Paediat Scand 1983:72:197-201	start of treatment in 27 patients with congenital hypothyroidism, some of whom were treated very early	- If treatment begins before 1 week of age, then IQ remains within normal range - Neurological damage seems to originate partly before birth, more serious injury arise if treatment is delayed >3/12 of age	Sample size small
8	Marti Virtaren et al *Finnish National Screening for Hypothyroidism* *Eur J Pediatr* 1984: 143: 2-5	Report of their screening programme in achieving a low frequency of false positive and early institution of treatment	- TSH screening supplemented by T4 in borderline samples - 1/2637 incidence - 0.08% false positive - median age at start of therapy 6 days	Good

No.	Author,Title, Journal Year	Study Type, Sample Size, Follow-up	Characteristics & Outcome	Comments & Grade of Evidence
SCREENING APPROACH IN NON-ASIAN REGION				
1	Fisher DA, Dussault JH, et al *Screening for Congenital hypothyroidism: Results of screening one million North American infants* J of Paediatr 1979, 94: 700 - 705	(i) Prospective study, consecutive newborns in 5 regions in N America over a 6 year period, n: one million	Birth prevalence 1: 3 684 1^o hypothyroidism 1: 4 254 2^o hypothyroidism 1: 68 200 Transient hypothyroidism 1: 37 370 TBG deficiency 1: 8 913 Recall rate for: (i) 1.1% (ii) 0.4% (iii) 0.17% (iv) 0.15% Treatment by 4-5 weeks	Fair Excellent study with detailed analysis of results with respect to: - type of thyroid disorders - advantages and disadvantages of each screening method discussed
2	Walfish P.G. *Evaluation of Thyroid-function screening tests for detecting neonatal hypothyroidism.* Lancet 1976;5:1208-1211	Prospective, newborns in Toronto, using either (i) filter spot T_4 (lower 6-10^{th} centile), 3-5 days, n: 6734 (ii) filter spot cord TSH	Incidence of CHT 1:5000 Recall rate for - 1.18% - 0.24% False positive rate - 3.5% - 0.19% Mean T_4 10.7 mcg/dL, 95% confidence range of 5.7 to 15.7 mcg/dL high recall rate due to high incidence of prematurity and low birth weight babies (18%)	Fair

No.	Author,Title, Journal Year	Study Type, Sample Size, Follow-up	Characteristics & Outcome	Comments & Grade of Evidence
		40-50 mu/mL n: 3733, at birth radioimmunoassay in both methods	Median TSH 8.7 mu/mL; babies with TSH 20-50 mu/mL are normal on follow up, all babies with CHT have TSH >70 mu/L. False positive recall related to perinatal stress TSH sensitive & specific	
3	M Virtanen, J. Perheentupa, J. Maenpaa et al *Finnish national screening for hypothyroidism* Eur J Paeds 1984;143:2-5	Prospective study n:175,188 Using Cord TSH (at birth) recall criteria: (i) TSH >44 mu/L (ii) TSH >59 mu/L (iii) TSH 45-59 mu/L (iv) T_4 <120	Incidence 1:2637 Recall rate (i) 0.24% (ii) 0.12% False positive (i) 0.21% (ii) 0.08% Treatment by 6 days	Fair

No.	Author,Title, Journal Year	Study Type, Sample Size, Follow-up	Characteristics & Outcome	Comments & Grade of Evidence
		mmol/L		
4	*Special Report: Newborn. Screening for metabolic disorders for in Australia and New Zealand: results for 1983* Med Aust 1985; 143:159-60J	Review data on screening programmes in Australia and New Zealand. Sample more than 4 million	Incidence of CHT 1 : 4253 in Australia and 1:4862 in New Zealand. Used T_4 with TSH on lowest T_4 or TSH	Poor
5	Grant DB *Screening for Congenital Hypothyroidism: the first decade.* Archive of Diseases in Children.	Review of scientific literature of screening methods in Europe and America	- Compares screening method using T_4 alone, T_4 with supplemental TSH or TSH - using T_4 alone is inadequate because high percentage of missed cases (30%) on cases with compensated 1^o hypothyroidism - T_4 with supplemental TSH has high recall rate, cost is cheaper - TSH is most sensitive, but expensive	Fair
6	Grant DB. Smith I *Survey of neonatal screening for primary hypothyroidism in England, Wales & Northern Ireland.*	Observational study. n: 1,941,146 in 25 screening laboratories using filter	- Overall incidence CHT 1: 2929 - Treatment by 17 days - Patient missed 0.8% (4/493 detected) - No mention of recall rate	Fair

No.	Author,Title, Journal Year	Study Type, Sample Size, Follow-up	Characteristics & Outcome	Comments & Grade of Evidence
	BMJ 1988; 296: 1355-1358	paper - TSH >10 mu/L (4 laboratories) - TSH >30 mu/L (2 regional centres) at 5-14 days of life radioimmunoassay/immunoradiometric assay		
7	Dussault JH, Morissette J, Higher *Sensitivity of Primary Thyrotropin in Screening for Congenital Hypothyroidism: A Myth?* J of Clin Endocrinol Metab 1983; 56: 849-855	Prospective, comparative study with different strategies using different diagnostic kits (i) T_4 <5 mcg/dl; n:93,000 (Micrometric neonatal T_4 kit)	Recall rate for: - T_4: 0.53% - TSH 25-50 mu/L • 0.21% (Phabedas) • 0.76% (Becton Dickinson); TSH >50 mu/L - 0.03% (Phabedas) - 0.46% (Becton Dickinson) Overall recall rate testing TSH was 0.27% for Phabedas and 1.2% for Becton – Dickinson 3 infants overall would have been missed using	Good

No.	Author,Title, Journal Year	Study Type, Sample Size, Follow-up	Characteristics & Outcome	Comments & Grade of Evidence
		(ii) TSH 25-50 mu/L n: 55,000 (Phabedas kit Pharnacia Diagnostic) n: 38,000 (Becton Dickinson immunodiagnostic TSH kit) (iii) TSH >50 mu/L; n: 55,000 (Phabedas); n: 38,000 (Becton Dickinson) Blood taken at 3 days of life	either approach 1 case of 2^o hypothyroidism detected by T_4 approach missed by TSH methodology False negative 3 cases using either approach T_4 methodology: Simple, cheap but have high recall rate at 0.5% TSH sensitivity depends on type of assay, Becton TSH kit high recall rate. 5-10% neonates with CHT missed using either approach.	
8	*American Academy of Paediatric Section on Endocrinology & Committee on Public Health.* *Newborn screening for congenital*	Recommendations by expert committee based on	Recommend blood taken within 2-6 days life. Using T_4 : - identified all forms of hypothyroidism and	Poor

No.	Author,Title, Journal Year	Study Type, Sample Size, Follow-up	Characteristics & Outcome	Comments & Grade of Evidence
	hypothyroidism recommended guidelines. Paediatrics 1993; 91(6): 1203 - 9	scientific data of screening in Europe, N.America, Japan. N.America used filter papter T_4 with TSH on low, or low normal T_4 (10-20th centile). Europe & Japan used TSH supplemented by T_4 for high TSH. n = 93,000	TBG deficiency. - recall rate high, 0.3% using T_4 alone; recall rate reduced to 0.05% using T_4 with TSH - 1:93,000 infant missed. Using TSH would : - miss 2^{o} hypothyroidism, TBG deficiency, delayed rise in TSH - recall rate low at 0.05%	

No	Author, Title, Journal Year	Study Type, Sample Size, Follow-up	Characteristics & Outcome	Comments & Grade of Evidence
SCREENING APPROACH IN NON-ASIAN REGION				
1	Lakhani M, Khurshid M, Naqvi SH, Akber M *Neonatal Screening For Congenital Hypothyroidism in Pakistan.* JPMA 39:282,1989	Observational study – results of screening programme in Karachi Sample size 5000	- Birth prevalence of congenital hypothyroidism in Karachi 1:1000. - Sample collection Heelprick capillary bloodspots on filter paper. Not mentioned on which day of life. Test : T4 and TSH Recall criteria Recall rate Confirmed cases 1. T4 <6.9, TSH >20 0.12% (6) 5/6 congenital hypothyroid 1/6 compensated hypothyroid 2. T4<6.9, TSH <20 6.0% (300) 1/9 TBG deficiency 3. T4 normal, TSH >20 1.3% (65) 1/9 compensated hypothyroid Established laboratory norm: Capillary blood T_4 6.9-26.4 ug/dl, TSH <20 uIU/ml; Venous blood T_4 4.5-12.5 ug/dl, TSH 0.3-4.5 uIU/ml Recall rate: - Prmary TSH screening - 1.42% (5 congenital hypothyroid) - Primary T4 screening - 6.12% (5 congenital	Poor Study design not clear. Very poor response to recall. High incidence, reasons not identified. ? endemic iodine deficiency. 2/5 had maternal history of thyroid disorder.

No	Author, Title, Journal Year	Study Type, Sample Size, Follow-up	Characteristics & Outcome	Comments & Grade of Evidence
			hypothyroid) - T4 & TSH screening - 7.42% (same result) Higher false positive and high recall rate if using primary T4 screening	
2	Rajatanavin R, Sriprapadaeng A, Sompong W, Kongsuksai A, Suebwonglee S, et al *Screening for Congenital Hypothyroidism in Thailand : Has Its Time Come?* J Med Assoc Thai. 1993; 76(2):2-8	Observational study- Results of screening programme. Sample size: 7 686 neonates	Birth prevalence 1: 3 843 Sample collection : cord blood. Test : TSH Coverage : 88% Recall criteria : TSH >30 uiu/ml Recall rate : 0.1% Missed cases : not mentioned. TSH > 5 uU/ml in 30% cases suggesting relative iodine deficiency.	Poor Presented distribution of serumTSH levels in all the neonates screened. 99^{th} percentile of TSH level : 20uiu/ml.
3.	LCK Low, HJ Lin, PT Cheung, FT Lee, TL Chu, et al *Screening for Congenital Hypothyroidism in Hong Kong.* Aust.Paediatr.J. 1986; 22:53-56.	Observational study-results of screening programme. Sample size : 20,319	Birth prevalence : 1: 2902 (7 confirmed CH, 2 transient) Sample collection: cord blood Test: TSH supplementary T4 Coverage: 99.38% Recall criteria : cord TSH > 15 uU/ml Recall rate: 5.4% Responses to recall: 71% Reasons: False addresses, parental refusal, taboos/ superstitions. Improved to 95% after publicity programme.	Poor Fairly large sample size. Frequency distribution of cord blood TSH levels given. Median value of cord blood TSH 5.8 uU/ml All cases of

No	Author, Title, Journal Year	Study Type, Sample Size, Follow-up	Characteristics & Outcome	Comments & Grade of Evidence
			TSH cut-off hypothyroid / T4 / Confirmed 15 low x2 7 (100%) 20 normal 6 (85.7%) 25 normal 5 (71.4%) Confirmation test Serum TSH > 40 uU/ml (2 occasions) Serum TSH 20-40 uU/ml & low or low normal T4 (3 occasions) False positives in difficult deliveries (vacuum, infant of diabetic mothers)	confirmed hypothyroidism had cord blood TSH above 97.4th percentile
4.	Desai MP, Colaco MP, Ajgaonkar AR, Mahadik CV, Vas FE, et al *Neonatal Screening for Congenital Hypothyroidism in a Developing Country : Problems and Strategies.* Indian J. Pediatr 1987; 54(4): 571-581	Observational study- Problems and strategies of neonatal congenital hypothyroid screening Sample size : 12,407	Birth prevalence CH=1:2481 livenirths Sample collection: cord blood Test: TSH with supplementary T4 when TSH >30 uU/ml Coverage: 72% Recall criteria: TSH >30 uU/ml Recall rate : 2.81% Response to recall : 30-100 % TSH 30-80 30% TSH >80 79% TSH >100 100% Cord TSH / Recall rate / Confirmed cases >30 uU/ml 2.81% 0 >80 uU/ml 0.38% 5 (100%)	Poor Demonstrated significant organisational, socio-economic, educational problems of the population. Study recommendation : to consider Cord TSH <50

No	Author, Title, Journal Year	Study Type, Sample Size, Follow-up	Characteristics & Outcome	Comments & Grade of Evidence
			TSH <300 uU/ml: no cong hypothyroid detected TSH >300 uU/ml : 5/7 hypothyroid 1/7 tansient hypothyroid, 1/7 normal. Mean cord TSH + 3SD = 5.069 +27.27 (term baby); = 5.069 + 19.19 (prem baby)	uU/ml safe; 50-100 uU/ml borderline, needs evaluation; >100 uU/ml
5.	Zhang YQ, Cao QX *Experience in Neonatal Screening for Congenital Hypothyroidism.* Chinese Medical Journal. 1993; 106(3):216-219.	Observational study- Results of neonatal hypothyroid screening programme. Sample size 91,683	Incidence of 1: 4,584 Sample collection: Heel prick capillary bloodspot 48-72 hours after birth 12 out of 20 (60%) cases of CH had low T4, high TSH 8 (40%) cases the serum T4 >77.4 nmol/L	Poor A large sample size
6.	Amar HSS, Jai Mohan *Screening for Congenital Hypothyroidism : A regional Pilot Project.* Health System Research Report 1977, Ipoh	Abstract - To determine the feasibilities of conducting a nation-wide screening	Birth prevalence 1:2983 Sample collection : cord blood Test : TSH complementary T4 Coverage : 91% (stillbirth, BBA, samples not collected, lysed or insufficienct blood) Recall criteria : TSH > 60 uU/ml or TSH 20-60	Poor Small sample Estimated cost of a national programmme using automated TSH

No	Author, Title, Journal Year	Study Type, Sample Size, Follow-up	Characteristics & Outcome	Comments & Grade of Evidence
	Hospital.	programme for CH, and identify problems associated with it. Sample size : 10,083	with T4 <68 nmol/L Recall rate : 0.11% TSH cut-off hypothyorid / Recall rate / Confirmed > 60 0.04% 3 / 4 25-60, T4<68 0.07% 0 / 6	chemiluminescent immunoassays RM 4 million/year.
7.	Amar HSS *Screening for Congenital Hypothyroidism in Southeast Asia.* Journal of Padiatrics, Obstetrics and Gynaecology Jan/Feb 1997:5-9	Review paper – highlight various factors in the SEA region that make screening programmes for CH a real challenge to institution	Pooled Birth Prevalence for SEA region 1 : 3093 Sample collection : - Heelprick bloodspots 3-8 days of life to avoid inconsistency in timing of neonatal surges of TSH. - Cord blood at birth : simple, acceptable, better coverage in SEA region, linked with G6Pd screening with no extra cost or manpower. Test: - T4, TSH supplement - TSH with T4 supplement - T4, TSH combined The majority of Asian programme uses primary TSH screening. Cord blood is the commonly used. Recall Rate: Primary TSH: 0.03 –0.8%	Poor Various issues in CH screening reviewed and major problems peculiar to SEA region discussed. Reported birth prevalence Singapore 1:2007 Hong Kong 1:2903 Thailand 1:3843 Malaysia 1:2634

No	Author, Title, Journal Year	Study Type, Sample Size, Follow-up	Characteristics & Outcome	Comments & Grade of Evidence
			Primary T4: 0.1-1.5% Missing cases: generally 5-10% whichever choice of approach is taken; due to deficiency of tests ; logistic errors	
8.	LL Wu, Sazali BS, N Adeeb, Khalid BAK *Congenital Hypothyroid Screening using Cordblood TSH. 1999* Singapore Med J. 1999; 40(1):23-26	A pilot study on neonatal hypothyroid screening in Kuala Lumpur Hospital Sample size :11,000	Birth prevalence 1:3,666 Sample collection : Dried cord blood on filter paper Test: TSH using commercial kit Recall criteria : TSH>20 miu/ml Recall rate 2.27% Response to recall : poor Median cord TSH : 4.83 mIU/ml Range of cord TSH (without hypothyroidism) : 0.5 – 77.5 uIU/ml	Poor Stressed on the need of increasing public awareness, good record keeping, up-dating addresses and contact numbers, improvement of logistics to ensure maximum cost-effectiveness of the programme.
9.	Harun F, Ch'ng SL *Congenital hypothyroid in a developing country. 1992.* Abstract in Clinical thyroidology,Innsbruck, Austria.	Observational study- Outcome of Pilot screening programme Sample size	Birth prevalence: 1 in 2410 newborn Sample collection: cord blood Test: TSH, T4 Recall criteria: Confirmed hypothyroid TSH>25 miu/ml	Poor

No	Author, Title, Journal Year	Study Type, Sample Size, Follow-up	Characteristics & Outcome	Comments & Grade of Evidence
		19,281	T4<80nmol/L; TSH>18miu/L) T4<55nmol/L; TSH<18miu/ml) 5/8 T4<80nmol/L; TSH<1.5 miu/L) Recall rate=1.7%	
10.	Joseph R, Ho LY, Gomez JM, Ikshuvanam M, AW TC, et al. *Non isotopic cord serum screening for congenital hypothyroidism in Singapore – the TSH and T4 Strategy.* Proceedings of the 8th International Neonatal Screening Symposium. New South Wales, Australia 12th- 15th Nov. 1991	Observational pilot study Sample size 20072 newborns	Birth prevalence : 1 in 2072 Sample collection: cord blood Test: TSH and T4 Coverage: 99.96% Recall criteria: Hypothyroid cases TSH>49.9 miu/ml 80% TSH 23-49.9 miu/L; T4<130 nmol/L 20% TSH 14-22.9 miu/ml; T4<92 nmol/L 0 TSH<14 miu/ml; T4<80 nmol/L 0 (in term infants with birth weight>2500G) Recall rate 3.3%	Poor
11.	M. Mafauzy, KE Choo, NA Rahman, M Musalmah, WB Wan Mohamad, BE	An observational	Birth prevalence 1:3065	Poor

	Author, Title, Journal Year	Study Type, Sample Size, Follow-up	Characteristics & Outcome	Comments & Grade of Evidence
	Mustaffa *Neonatal Screening For Congenital Hypothyroidism in North-Eastern Peninsular Malaysia.* Journal of AFES (13) 1&2	pilot study Sampale size 12,261	Sample collection: cord blood Test: T4 & TSH Criteria for recall: Hypothyoroid cases TSH > 30 uIU/ml 1.2% 2 T4 < 50 nmol/L 0.6% 2 Recall rate: 1.8% (total) Response to recall: 73.7% Mean cord T4 121 nmol/L (range 93-149 nmol/L) Mean cord TSH 8.9 uIU/ml (range 3.0-14.8 uIU/ml)	

Appendix A

LEVELS OF EVIDENCE SCALE

Level	Strength of Evidence	Study Design
1	Good	Meta-analysis of RCT, Systematic reviews.
2	Good	Large sample of RCT
3	Good to fair	Small sample of RCT
4		Non-randomised controlled prospective trial
5	Fair	Non-randomised controlled prospective trial with historical control
6	Fair	Cohort studies
7	Poor	Case-control studies
8	Poor	Non-controlled clinical series, descriptive studies multi-centre
9	Poor	Expert committees, consensus, case reports, anecdotes

SOURCE: ADAPTED FROM CATALONIAN AGENCY FOR HEALTH TECHNOLOGY ASSESSMENT (CAHTA), SPAIN.

Appendix B

LOCAL COST IMPLICATIONS

1. Number of live births (1997) – 523,324
2. Incidence of Congenital Hypothyroidism 1: 3000 per year
3. Estimated No of babies born with Congenital Hypothyroidism per year (1998)
   = (1 / 3 000) X 523 394
   = 1 74.5
   = 175
4. No of mentally retarded children according to severity
   - Severe =
   - Moderate =
   - Mild =
5. Estimated G.N.P (1997) = RM 12 102 per capita
6. Life expectancy at birth (1998) in years
   - Male = 69.3
   - Female = 74.1
   - Average = 71.7
   - Years of productivity = 71.7 - 15
     = 56.7 years

Estimated Costing

1. Total cost of screening for Congenital Hypothyroidism
   - Total births per year = 523 394
   - Cost of reagents = RM 6.00/test
   - Cost for screening = 523 394 X 6
     = **RM 3 140 634 .00**
   - Cost for recall = 1% X 6 X 523 394
     = **RM 31 403.64**
   - Total Cost = **RM 3 172037 .64 /year**

2. Total cost of treatment
   - RM 3.00/per month X 12 = RM 36.00/year/case
   - RM 36.00 X 175 cases = RM 5 652.00/year / all cases
   - RM 36.00 X 71.7 = RM 2 5812/case/life span
   - RM 36.00 X 175 X 71.7 = RM 451 710.00/lfe span/ all cases

3. Loss of productivity (Per Capita GNP) for cases
   - Loss of GNP due to hypothyroidism
     = RM 12 102 X 56.7
     = RM 686 183.40/case/lifespan

- Annual loss = RM 12 102 X 175
  = RM 2 117 850.00/year

4. Loss of GNP for mothers
   - No of severe mentally retarded cases
   - No of moderate mentally retarded cases

5. Costing of Special schools for
   - Severe mentally retarded cases
   - Moderate mentally retarded cases
   - Mild mentally retarded case

THE FOLLOWING HTA REPORTS ARE AVAILABLE ON REQUEST:

REPORT	**YEAR**
1. LOW TEMPERATURE STERILISATION	1998
2. DRY CHEMISTRY	1998
3. DRY LASER IMAGE PROCESSING	1998
4. ROUTINE SKULL RADIOGRAPHS IN HEAD INJURY PATIENTS	2002
5. STROKE REHABILITATION	2002
6. MEDICAL MANAGEMENT OF SYMPTOMATIC BENIGN PROSTATIC HYPERPLASIA	2002
7. CHILDHOOD IMMUNISATION	2002
8. ROUTINE NEONATAL VITAMIN K ADMINISTRATION AT BIRTH	2002
9. USE OF POLYMERASE CHAIN REACTION IN LABORATORY TESTING	2002
10. SCREENING FOR CONGENITAL HYPOTHYROIDISM	2002
11. SCREENING FOR DIABETIC RETINOPATHY	2002